Impact of Positive Surgical Margins on Overall Survival after Partial Nephrectomy, a Matched Comparison Based on the National Cancer Database

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Highlights

- Using the National Cancer Database, we performed a matched comparison between positive and negative surgical margins after partial nephrectomy for localized renal cell carcinoma.
- Patients with positive surgical margins in partial nephrectomy have significantly worse overall survival.
- Old age, high comorbidity score and large tumor size are also associated with higher hazard ratios for all-cause mortality, while papillary and chromophobe histology subtypes have lower hazard ratios.

Introduction

The impact of positive surgical margins (PSM) in partial nephrectomy (PN) has been a controversy. Previous studies on the relationship between PSM and overall survival (OS) were either underpowered or had highly dissimilar groups. We used the National Cancer Database with propensity score matching to determine the association between PSM and OS after PN.

Materials and Methods

We identified patients with T1/T2N0M0 renal cancer treated with PN between 2004 and 2009, and divided them into 2 groups based on their margin status. We used propensity score matching to ensure similarities in age, comorbidity score (CCI), tumor size,

histology and grade between groups. Covariates were compared by χ^2 test. Cox multiple regression was used to estimate the hazard ratios (HR) for all-cause mortality. OS between matched groups were compared by log-rank, Breslow and Tarone-Ware tests.

Results

After excluding those with missing data on margin or survival status, 20762 patients were eligible for matching. Each matched group had 1265 patients, similar in age, gender, race, CCI, tumor size, histology and grade. There were 386 recorded all-cause mortalities over a median follow-up duration of 72.6 months. Cox multiple regression showed a higher risk of all-cause mortality among cases with PSM (HR: 1.393, p=0.001). Old age, high CCI and large tumors had higher risks, while papillary and chromophore histologic subtypes had lower risks. PSM was associated with significantly worse OS by log-rank, Breslow and Tarone-Ware tests.

Conclusion

PSM is associated with significantly worse OS after PN.

Keywords

positive surgical margins; overall survival; partial nephrectomy; matched comparison; National Cancer Database

Introduction

The impact of positive surgical margins (PSM) in partial nephrectomy (PN) has been a controversy. Various studies showed conflicting results regarding the associations between PSM and progression-free,[1 – 7] cancer-specific,[5, 8, 9] as well as overall survivals (OS).[5, 8, 10] A multi-centered study[5] and a study based on the Ontario Cancer Registry[8] found no associations between PSM and OS, but the statistical powers of both studies were limited by small sample sizes. A more recent study based on the National Cancer Database (NCDB) involved a cohort of 6038 patients who underwent PN for clinical T1 or T2 disease, and found PSM to be associated with an increased risk of all-cause mortality.[10] However, the PSM group in this study had significantly older patients with higher comorbidity scores compared to the negative surgical margins (NSM) group, so there might be confounding effects from other covariates. To determine the association between PSM and OS, a study that has a large sample size yet similar groups for comparison would be ideal.

Therefore, we used the latest NCDB participant user file (PUF) to determine if PSM has an impact on OS after PN in the contemporary clinical setting, with statistical matching to ensure similarities in key covariates between groups.

Materials and Methods

The institutional review board approved this study (protocol number: 1611211043, approval date: December 7, 2016).

We used the NCDB PUF spanning from 2004 to 2014. To ensure that all cases for analysis had a minimum of 5 years of follow-up after PN, we only included cases between 2004 and 2009. Patients with renal cell carcinoma (RCC) were identified as those who carried the code C649 for the data item 'Primary Site', based on the International Classification of Diseases for Oncology, 3rd Edition.[11] Among these cases, we selected those with clinical T1 or T2 N0M0 disease according to data items 'AJCC Clinical T', 'AJCC Clinical N' and 'AJCC Clinical M', based on the American Joint Committee on Cancer Stage Manual, 7th Edition.[12] The cases were screened to identify those treated with PN, according to the data item 'Surgical Procedure of the Primary Site at any CoC Facility' with the code 30 representing PN, and were classified into two groups based on surgical margin status. Duration of follow-up was defined by the data item ''Last Contact or Death, Months from Dx' as the time between the date of initial diagnosis and the date on which the patient was last contacted or died, and survival status at the end of follow-up was defined by the data item 'PUF Vital Status'. Patients with missing data on surgical margin status or survival status were excluded.

The endpoint of our study was OS in the PSM and NSM groups. Covariates included age, gender, race, Charlson-Deyo comorbidity score (CCI), tumor size, histology and grade. Figure 1 summarizes the process of patient selection prior to statistical matching.

We recoded ratio covariates into clinically meaningful categories for statistical analysis. We first performed multivariate logistic regression to identify predictors for PSM. This was followed by propensity score matching with fuzz factor set at 0, giving priority to exact matches and without replacement in sampling, to produce a PSM and a NSM group with matches for age, CCI, tumor size, histology and grade. Covariates were

compared between groups by χ^2 test, with relevant Cramer's V values to reflect effect sizes. Cox multiple regression was then used to estimate the hazard ratios (HR) of the covariates for all-cause mortality. Log-rank, Breslow and Tarone-Ware tests were used to compare OS between matched groups. Further analyses were done among patients of specific age or with specific CCI, tumor size, histology and grade to determine the effects of PSM in these subgroups. All statistical analyses were done using SPSS version 24.0 (IBM Corp., Armonk, NY). A p value of <0.05 defined statistical significance throughout the study.

Results

A total of 21243 patients with T1 or T2 N0M0 RCC between 2004 and 2009 underwent PN. Among them, 475 patients had unknown surgical margin status and were excluded. Of the remaining 20768 patients, 1279 had PSM and 19489 had NSM. One patient from the PSM group and 5 patients from the NSM group were excluded due to missing data on survival status. Therefore, 1278 PSM and 19484 NSM patients were eligible for statistical matching. Propensity score matching produced two groups highly similar in age, gender, race, CCI, tumor size, histology and grade, with 1265 patients in each group. Table 1 illustrates the descriptive statistics before and after statistical matching.

Compared to the reference category of age below 50 years, most other categories of age had statistically significant odds ratios (OR) above 1 for PSM. Increasing age appeared to be associated with higher odds for PSM, with OR up to 1.800 among those aged 80 years and above. Papillary and chromophobe tumors, as well as Fuhrman

grade 3 or 4 tumors, also had statistically significant OR above 1 for PSM compared to their respective reference categories. Table 2 illustrates the multivariate logistic regression model estimating the ORs for PSM among the various categories of covariates in our study.

After matching, the mean follow-up duration was 70.3 months (median: 72.6 months), with 386 recorded all-cause mortality. Cox multiple regression showed that PSM was associated with a higher risk of all-cause mortality compared to NSM (HR: 1.393, *p*=0.001). There was a clear trend showing increasing risks of all-cause mortality proportional to age. Compared to tumors 4cm and below, tumors above 4cm up to 7cm and tumors above 7cm up to 10cm were associated with increased risks of all-cause mortality (HR: 1.592, 2.639; p<0.001, =0.003 respectively). Tumors above 10cm had a HR of 3.548 though this was not statistically significant, likely due to the very low numbers within this category after matching. Compared to CCI of 0, CCI of 1 was not associated with a significantly higher risk of all-cause mortality, while CCI of 2 and above had a statistically significant HR of 2.384 (p<0.001).

With reference to clear cell RCC, papillary and chromophobe tumors were associated with decreased risks of all-cause mortality (HR: 0.719, 0.341; p=0.020, <0.001 respectively). Sarcomatoid tumors had a HR of 1.724 though this was not statistically significant, again likely due to the very low numbers within this category after matching. Gender, race and tumor grade did not seem to have significantly different HRs for all-cause mortality compared to their respective reference categories. Table 3 illustrates the Cox multiple regression model estimating the HRs for all-cause mortality among the various categories of covariates in our study.

Log-rank, Breslow and Tarone-Ware tests showed significantly worse OS in patients with PSM compared to those with NSM, with p-values of 0.003, 0.011 and 0.006 respectively. Figure 2 represents the Kaplan-Meier curves for OS stratified by surgical margin status.

PSM appeared to have significantly adverse impact on OS among patients aged 70 years and above, with CCI of 1, tumor size 4cm and below and clear cell RCC. It also exerted adverse impacts on OS across all categories of tumor grades. Table 4 illustrates the HRs for all-cause mortality due to PSM among patients in specific subgroups of age, CCI, tumor size, histology and grade, with reference to those with NSM in the same subgroups.

Discussion

The basis of PN is nephron preservation, which is associated with improved post-operative renal function, reduced renal and cardiovascular complications and better OS.[13, 14] On the oncologic aspect, PN has an incidence of PSM ranging from 0 to 7%,[15] which is much higher than that of radical nephrectomy.[16] Nonetheless, PN has surpassed RN as the standard surgical option for most localized renal tumors.[17, 18]

The clinical impact of PSM in PN has been a controversy. Various multi-centered studies have made conflicting conclusions on whether PSM results in an increased risk of tumor recurrence.[1 – 3, 5, 6] Interestingly, most studies found no impact on cancer-specific survival by PSM.[5, 8, 9] It is possible that PSM is associated with increased tumor recurrence without compromising cancer-specific survival due to the slow growth rate of

any microscopic residual tumor cells, since the mean annual growth rate of radiologically evident small renal masses is about 0.28cm.[19] It takes a long time for any recurrences to be clinically detectable, and an even longer time to cause cancer-related mortality.

A long duration between PN and any subsequent deaths implies that such mortality is prone to various clinical and non-clinical factors beyond cancer related ones. As such, without discounting the clinical importance of other survivals, OS should also be regarded as one of the more relevant quality control measures after PN. Our study does not include progression-free and cancer-specific survivals as endpoints, due to limitations of the NCDB, but our finding of PSM being associated with a higher risk of all-cause mortality emphasizes the clinical need to reduce PSM at all cost during PN, amidst the various reports that PSM does not affect tumor recurrence and cancer-specific survival.[1, 4, 5, 6, 8, 9]

Prior to our findings, only one other study found PSM to have significant impact on OS after PN.[10] This study by Maurice MJ et al was also based on the NCDB and included patients with clinical T1 or T2 N0M0 RCC treated with PN between 2003 and 2006. They found that PSM had a statistically significant HR of 1.35 for all-cause mortality. However, their initial univariate analysis showed that patients in the PSM group were significantly older with higher CCI. The tumors in their PSM and NSM groups were also significantly different in pathologic T-stage. The authors then performed multivariate logistic regressions analyses, which showed that CCI and pathologic T-stage were associated with both PSM and OS. These associations raised the possibility of significant confounding by CCI and pathologic T-stage when they drew the conclusion

that PSM was associated with poorer OS. Their findings prompted us to re-assess the statistical approach towards making comparisons using data from the NCDB.

The occurrence of PSM in PN is associated with various clinical factors. The multi-centered Registry of Conservative Renal Surgery project by 19 Italian urology centers found increased risks of PSM in patients who were older, with upper pole tumors or with Fuhrman grade 3 or 4 tumors.[20] Similarly, our study found that older patients and those with Fuhrman grade 3 or 4 tumors had increased risks for PSM. The Surveillance and Treatment Update Renal Neoplasms study found an increased risk of PSM in PN compared to simple enucleation in univariate analysis. However, its PN group consisted of patients with larger and higher grade tumors, treated by institutions with lower caseloads, and no further analysis was done to reduce confounding.[21] Kwon EO et al found imperative indication for PN to be the only significant factor associated with an increased risk of PSM in their multivariate analysis,[7] though this may not be clinically relevant since PN indications are no longer classified into ‘absolute’, ‘relative’ and ‘elective’. Ani I et al found perinephric fat invasion to be a significant factor for PSM, but pathologic T3-stage tumors did not have statistically significant increased HR in the same multivariate logistic regression model.[8] Our finding that papillary and chromophobe tumors had increased risks for PSM compared to clear cell RCC appeared counter-intuitive. Without further details on the use of pre-operative biopsy and the proportion of cases treated by enucleation, it was difficult to pinpoint why certain histologic subtypes had increased PSM risks.

Based on the findings of these studies, we decided that statistical matching should be performed for age, CCI, tumor size, histology and grade. Since the NCDB does not

contain information like surgical approach, tumor configuration and nephrometry scores, these could not be matched. Nonetheless, propensity score matching resulted in high similarities between our PSM and NSM groups, with perfect matches in key covariates like age, CCI, tumor size, histology and grade.

Subgroups analyses in our study found that OS in certain categories of patients, such as the elderly, those with clinical T1a tumors and clear cell RCC, are especially prone to the adverse impacts of PSM. Interestingly, while Cox multiple regression did not find a higher HR for all-cause mortality in high grade tumors compared to low grade ones, subgroup analyses revealed that PSM exerted adverse impacts on OS across all tumor grades. This highlights the importance to avoid PSM even if pre-operative imaging describes a localized small renal mass or pre-operative biopsy suggests a low grade tumor. Such importance is also applicable among elderly patients, despite the common belief that many of these patients may die with RCC rather than from RCC when there is residual tumor after PN. Due to low numbers, clinical T2a and T2b tumors were combined as a single category in subgroup analysis, though the HR for all-cause mortality due to PSM in this newly formed category still did not achieve statistical significance.

To the best of our knowledge, our study has the largest matched groups to determine the impact of PSM on OS after PN. However, it is not without limitations. Like any other studies based on a retrospective dataset, our findings were vulnerable to any inaccuracies in the NCDB. Statistical matching only accounted for covariates available in the NCDB, and confounding could still occur from various unknown clinical factors. While propensity score matching helped to reduce selection bias and confounding, a

large number of patients with NSM were excluded after matching, significantly reducing the effects of the matched covariates on OS. This is probably the reason that our Cox multiple regression model did not produce statistically significant HRs for gender, race, tumor grade and certain categories of CCI, tumor size and histology, while that by Maurice MJ et al showed some of these covariates as significant factors impacting OS.[10] However, since the primary goal of our study is to determine the effect of PSM on OS, this did not weaken the validity of our conclusion. Longer follow-ups would also be ideal when studying OS after PN, as the number of mortality in the entire matched cohort up to 140 months of follow-up was low (386 deaths in 2530 patients).

Conclusions

Our study found that PSM is associated with worse OS after PN, at 72.6 month median follow-up. It emphasized the clinical importance to maintain a low PSM rate in PN, despite various studies showing conflicting results regarding the impact of PSM on progression-free and cancer-specific survivals.

Acknowledgements

The NCDB is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It is a nationally recognized clinical oncology database sourced from hospital registry data that are collected in more than 1,500 CoC-accredited facilities, jointly sponsored by the American College of

Surgeons and the American Cancer Society. Data represent more than 70 percent of newly diagnosed cancer cases nationwide and more than 34 million historical records. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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Tables and Figures

Figure 1. Diagram showing the process of patient selection for propensity score matching. (RCC: renal cell carcinoma, ICD-O-3: International Classification of Diseases for Oncology, 3rd Edition, NCDB: National Cancer Database, PUF: participant user file, AJCC: American Joint Committee on Cancer, PN: partial nephrectomy, PSM: positive surgical margins, NSM: negative surgical margins)

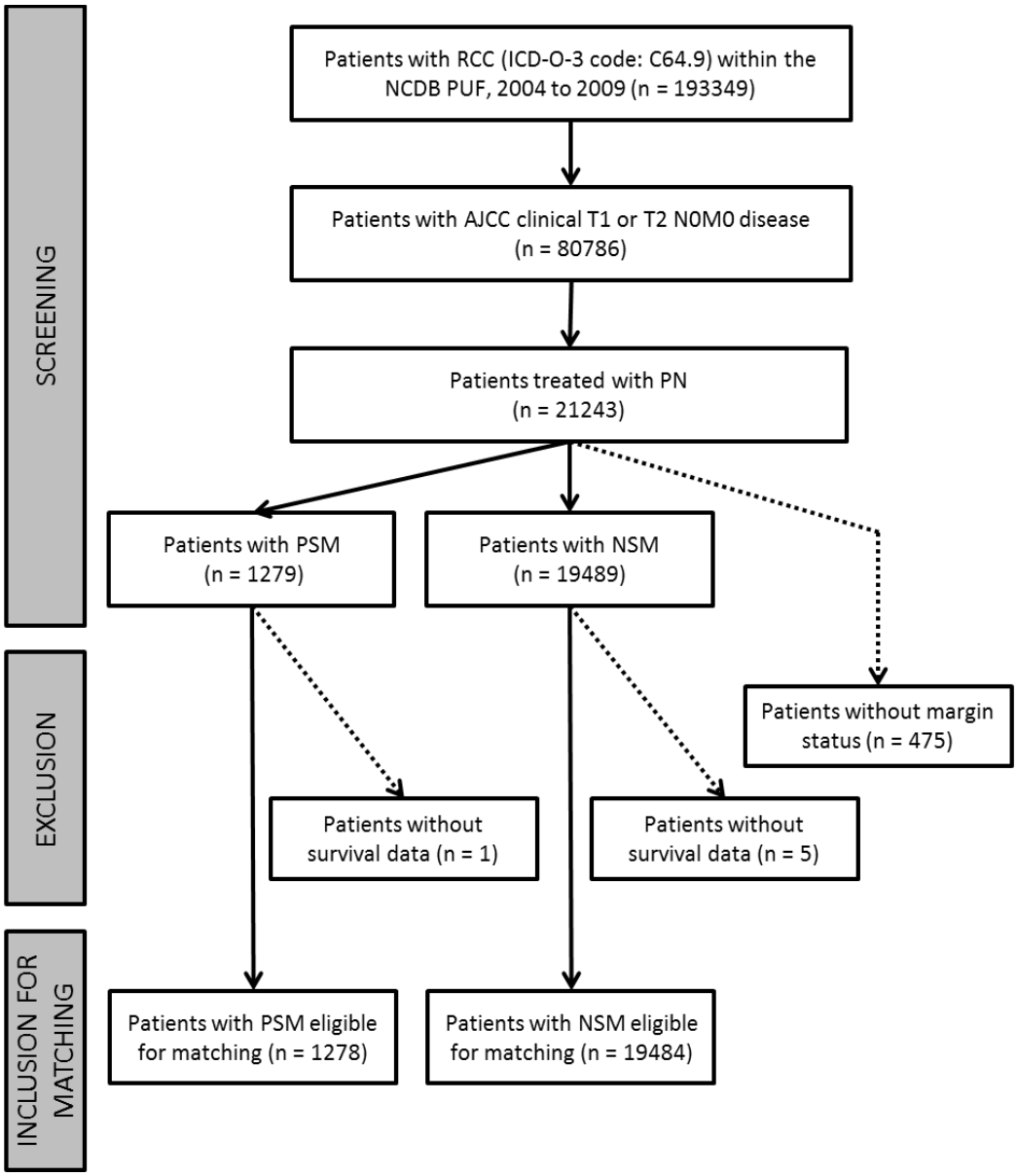

Table 1. Descriptive statistics before and after propensity score matching, shown as absolute number (percentage). (PSM: positive surgical margins, NSM: negative surgical margins, φ_C: Cramer's V values, CCI: Charlson-Deyo comorbidity score)

		Before propensity score matching				**After propensity score matching**			
		PSM (n=1278)	NSM (n=19484)	φ_C	*p*-value	PSM (n=1265)	NSM (n=1265)	φ_C	*p*-value
Age (year)	< 50	262 (20.5%)	4801 (24.6%)	0.036	<0.001	260 (20.6%)	260 (20.6%)	0	1.000
	50 – 59	332 (26.0%)	5323 (27.3%)			331 (26.2%)	331 (26.2%)		
	60 – 69	377 (29.5%)	5497 (28.2%)			374 (29.6%)	374 (29.6%)		
	70 – 79	242 (18.9%)	3235 (16.6%)			238 (18.8%)	238 (18.8%)		
	≥ 80	65 (5.1%)	628 (3.2%)			62 (4.9%)	62 (4.9%)		
Gender	Male	816 (63.8%)	11929 (61.2%)	0.013	0.062	808 (63.9%)	788 (62.3%)	0.016	0.410
	Female	462 (36.2%)	7555 (38.8%)			457 (36.1%)	477 (37.7%)		
Race	White	1017 (79.6%)	15650 (80.3%)	0.013	0.497	1007 (79.6%)	995 (78.7%)	0.036	0.521
	Black	148 (11.6%)	2026 (10.4%)			146 (11.5%)	137 (10.8%)		
	Hispanic	62 (4.9%)	1044 (5.4%)			62 (4.9%)	74 (5.8%)		
	Others	30 (2.3%)	504 (2.6%)			30 (2.4%)	41 (3.2%)		
	Unknown	21 (1.6%)	260 (1.3%)			20 (1.6%)	18 (1.4%)		
CCI	0	891 (69.7%)	14169 (72.7%)	0.018	0.037	887 (70.1%)	887 (70.1%)	0	1.000
	1	292 (22.8%)	4130 (21.2%)			290 (22.9%)	290 (22.9%)		
	≥ 2	95 (7.4%)	1185 (6.1%)			88 (7.0%)	88 (7.0%)		
Tumor size (cm)	≤ 4	1062 (83.1%)	16094 (82.6%)	0.009	0.771	1059 (83.7%)	1059 (83.7%)	0	1.000
	> 4 – ≤ 7	186 (14.6%)	2842 (14.6%)			181 (14.3%)	181 (14.3%)		
	> 7 – ≤ 10	20 (1.6%)	376 (1.9%)			19 (1.5%)	19 (1.5%)		
	> 10	4 (0.3%)	95 (0.5%)			2 (0.2%)	2 (0.2%)		
	Unknown	6 (0.5%)	77 (0.4%)			4 (0.3%)	4 (0.3%)		
Histology	Clear cell	866 (67.8%)	14632 (75.1%)	0.044	<0.001	865 (68.4%)	865 (68.4%)	0	1.000
	Papillary	254 (19.9%)	3169 (16.3%)			252 (19.9%)	252 (19.9%)		
	Chromophobe	114 (8.9%)	1137 (5.8%)			108 (8.5%)	108 (8.5%)		

	Collecting duct	0	17 (0.1%)			0	0		
	Sarcomatoid	3 (0.2%)	39 (0.2%)			2 (0.2%)	2 (0.2%)		
	Others	41 (3.2%)	490 (2.5%)			38 (3.0%)	38 (3.0%)		
Fuhrman grade	1 – 2	857 (67.1%)	13638 (70.0%)	0.023	0.005	852 (67.4%)	852 (67.4%)	0	1.000
	3 – 4	283 (22.1%)	3604 (18.5%)			278 (22.0%)	278 (22.0%)		
	Unknown	138 (10.8%)	2242 (11.5%)			135 (10.7%)	135 (10.7%)		

Table 2. Multivariate logistic regression estimating the ORs of PSM among the various categories of covariates before propensity score matching. (PSM: positive surgical margins, CCI: Charlson-Deyo comorbidity score, OR: odds ratio, CI: confidence interval, Ref: reference)

		OR for PSM	95% CI	*p*-value
Age (year)	< 50	1.0 (Ref)		
	50 – 59	1.101	0.930 – 1.302	0.263
	60 – 69	1.188	1.007 – 1.401	0.041
	70 – 79	1.294	1.077 – 1.556	0.006
	≥ 80	1.800	1.350 – 2.401	<0.001
Gender	Male	1.0 (Ref)		
	Female	0.915	0.812 – 1.032	0.148
Race	White	1.0 (Ref)		
	Black	1.088	0.907 – 1.305	0.363
	Hispanic	0.984	0.755 – 1.284	0.906
	Others	0.940	0.646 – 1.367	0.745
	Unknown	1.285	0.819 – 2.015	0.276
CCI	0	1.0 (Ref)		
	1	1.101	0.958 – 1.264	0.175
	≥ 2	1.242	0.995 – 1.552	0.056
Tumor size (cm)	≤ 4	1.0 (Ref)		
	> 4 – ≤ 7	0.910	0.773 – 1.072	0.259
	> 7 – ≤ 10	0.711	0.450 – 1.122	0.143
	> 10	0.572	0.209 – 1.562	0.275
	Unknown	1.175	0.509 – 2.711	0.705
Histology	Clear cell	1.0 (Ref)		
	Papillary	1.299	1.118 – 1.509	0.001
	Chromophobe	1.756	1.422 – 2.167	<0.001

	Collecting duct	0	0	0.998
	Sarcomatoid	1.274	0.392 – 4.148	0.687
	Others	1.359	0.979 – 1.887	0.066
Fuhrman grade	1 – 2	1.0 (Ref)		
	3 – 4	1.185	1.028 – 1.366	0.019
	Unknown	0.868	0.717 – 1.051	0.147

Table 3. Cox multiple regression estimating the HRs for all-cause mortality among the various categories of covariates after propensity score matching. (NSM: negative surgical margins, PSM: positive surgical margins, CCI: Charlson-Deyo comorbidity score, HR: hazard ratio, CI: confidence interval, Ref: reference)

		HR for all-cause mortality	95% CI	*p*-value
Margin status	NSM	1.0 (Ref)		
	PSM	1.393	1.138 – 1.705	0.001
Age (year)	< 50	1.0 (Ref)		
	50 – 59	2.341	1.422 – 3.854	0.001
	60 – 69	4.027	2.525 – 6.423	<0.001
	70 – 79	6.721	4.214 – 10.720	<0.001
	≥ 80	13.880	8.359 – 23.048	<0.001
Gender	Male	1.0 (Ref)		
	Female	0.839	0.675 – 1.044	0.116
Race	White	1.0 (Ref)		
	Black	1.176	0.842 – 1.641	0.341
	Hispanic	1.095	0.678 – 1.769	0.710
	Others	0.888	0.454 – 1.739	0.729
	Unknown	0.567	0.181 – 1.771	0.329
CCI	0	1.0 (Ref)		
	1	1.165	0.917 – 1.480	0.211
	≥ 2	2.384	1.766 – 3.218	<0.001
Tumor size (cm)	≤ 4	1.0 (Ref)		
	> 4 – ≤ 7	1.592	1.237 – 2.049	<0.001
	> 7 – ≤ 10	2.639	1.396 – 4.990	0.003
	> 10	3.548	0.490 – 25.710	0.210
	Unknown	0.000	0 – 1.008×10^{91}	0.931

Histology	Clear cell	1.0 (Ref)		
	Papillary	0.719	0.544 – 0.949	0.020
	Chromophobe	0.341	0.200 – 0.580	<0.001
	Sarcomatoid	1.724	0.238 – 12.473	0.590
	Others	0.648	0.332 – 1.264	0.203
Fuhrman grade	1 – 2	1.0 (Ref)		
	3 – 4	1.050	0.822 – 1.342	0.694
	Unknown	1.515	1.095 – 2.097	0.012

Figure 2. Kaplan-Meier curves showing OS stratified by surgical margin status. (PSM: positive surgical margins, NSM: negative surgical margins)

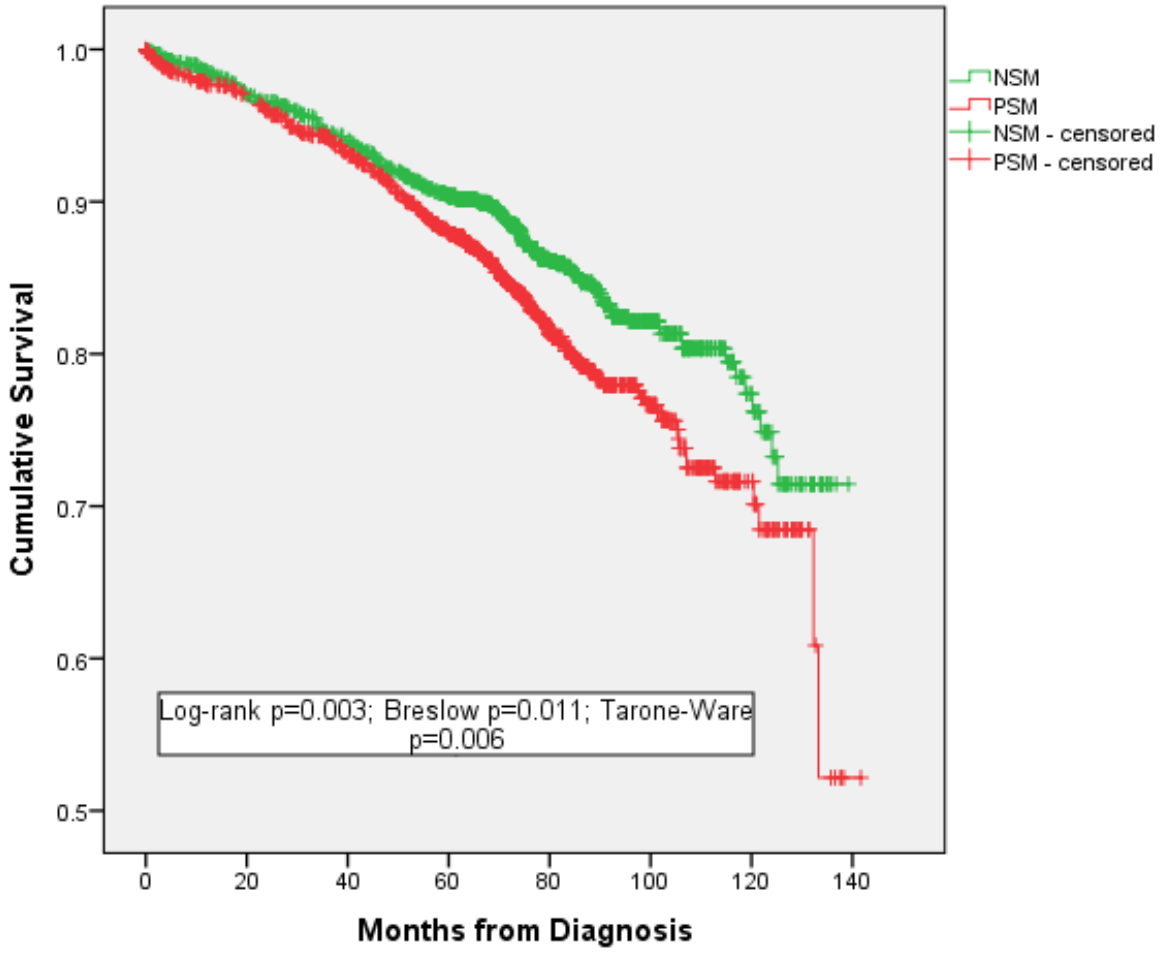

Table 4. Subgroup analyses estimating the HRs for all-cause mortality between PSM and NSM among patients with specific age, CCI, tumor size, histology and grade. (PSM: positive surgical margins, NSM: negative surgical margins, CCI: Charlson-Deyo comorbidity score, CI: confidence interval, Ref: reference)

		HR for all-cause mortality due to PSM (Ref = 1.0 NSM)	95% CI	p-value
Age (year)	< 50	0.746	0.304 – 1.835	0.524
	50 – 59	1.407	0.837 – 2.366	0.197
	60 – 69	1.136	0.795 – 1.624	0.485
	70 – 79	1.559	1.082 – 2.244	0.017
	≥ 80	1.969	1.109 – 3.497	0.021
CCI	0	1.065	0.823 – 1.379	0.632
	1	2.395	1.565 – 3.667	<0.001
	≥ 2	1.414	0.812 – 2.463	0.221
Tumor size (cm)	≤ 4	1.384	1.098 – 1.744	0.006
	> 4 – ≤ 7	1.241	0.786 – 1.959	0.354
	> 7	4.829	0.781 – 29.849	0.090
Histology	Clear cell	1.423	1.129 – 1.793	0.003
	Papillary	1.335	0.809 – 2.204	0.258
	Chromophobe	0.788	0.270 – 2.300	0.663
Grade	1 – 2	1.365	1.061 – 1.756	0.015
	3 – 4	1.779	1.150 – 2.750	0.010

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